

I. Analysis with Data Pooled Across Centers

	Erythema			Pruritus			Overall Severity		
	Time	Met vs Veh	p	Time	Met vs Veh	p	Time	Met vs Veh	p
ANOVA-1	wk10	Score 1.3 vs 1.7	0.01	wk 2	%↓ 58 vs 85	0.01	wk10	Score 1.3 vs 1.8	<0.01
	wk10	↓ 0.9 vs 0.5	<0.01	wk10	%↓ 98 vs 64	<0.01	wk10	↓ 0.8 vs 0.4	<0.01
	wk10	%↓ 42 vs 25	<0.01				wk10	%↓ 38 vs 18	<0.01
ANOVA-2 (nonpara- metric)	wk 7	↓ 0.8 vs 0.5	0.03	wk10	↓ 0.4 vs 0.2	0.04	wk10	Score 1.3 vs 1.8	<0.01
	wk10	Score 1.3 vs 1.7	<0.01				wk10	↓ 0.8 vs 0.4	<0.01
	wk10	↓ 0.9 vs 0.5	<0.01						
ANCOVA-1	wk10	Score 1.3 vs 1.7	<0.01				wk10	Score 1.3 vs 1.8	<0.01
ANCOVA-2	wk10	Score 1.3 vs 1.6	0.02				wk10	Score 1.3 vs 1.8	<0.01

*Week-10 and Endpoint analyses gave identical results. Met=metronidazole, Veh=vehicle. Score graded 0=none, 1=mild, 2=moderate, 3=severe. ↓=reduction in score, %↓=percent reduction in score. ANOVA-1: using parametric analysis. ANOVA-2: Friedman's nonparametric analysis. ANCOVA-1: using baseline scores as covariate. ANCOVA-2: using baseline papule+pustule counts as covariate.

II. Analysis excluding Centers with Significant Treatment-Investigator Interactions

	Erythema			Pruritus			Overall Severity		
	Time	Met vs Veh	p	Time	Met vs Veh	p	Time	Met vs Veh	p
ANOVA (minus Dr. Hino)	wk 7	↓ 0.8 vs 0.5	0.04	wk 2	%↓ 63 vs 100	0.02	wk10	Score 1.3 vs 1.8	<0.01
	wk10	Score 1.3 vs 1.7	0.04	wk10	%↓ 100 vs 42	0.02	wk10	↓ 0.8 vs 0.3	<0.01
	wk10	↓ 0.9 vs 0.5	0.01				wk10	%↓ 37 vs 15	<0.01
	wk10	%↓ 41 vs 23	0.02						
ANOVA (minus Dr. Stewart)	wk 2	↓ 1.8 vs 2.0	0.04				wk 7	Score 1.4 vs 1.7	0.04
	wk10	Score 1.2 vs 1.7	<0.01				wk 7	↓ 0.8 vs 0.5	0.02
	wk10	↓ 1.0 vs 0.5	<0.01				wk 7	%↓ 36 vs 23	0.03
	wk10	%↓ 45 vs 23	<0.01				wk10	Score 1.3 vs 1.8	<0.01
							wk10	↓ 0.8 vs 0.4	<0.01
							wk10	%↓ 39 vs 17	<0.01
ANCOVA (minus Dr. Hino)	wk10	Score 1.3 vs 1.7	0.02	wk10	Score <0.1 vs 0.1	0.03	wk10	Score 1.3 vs 1.8	<0.01
ANCOVA (minus Dr. Stewart)	wk 2	Score 1.8 vs 2.0	0.04				wk 7	Score 1.4 vs 1.7	0.02
	wk10	Score 1.2 vs 1.7	<0.01				wk10	Score 1.3 vs 1.8	<0.01

*Week-10 and Endpoint analyses gave identical results. Met=metronidazole, Veh=vehicle. Score graded 0=none, 1=mild, 2=moderate, 3=severe. ↓=reduction in score, %↓=percent reduction in score. ANOVA: using parametric analysis. ANCOVA: using baseline scores as covariate.

Comment Most of the secondary variable data support those of primary variables at endpoint. However, the percent reductions in the following clinical signs and symptoms only sporadically showed significant differences between the treatment groups and comparison of the differences at endpoint did not reveal significance: telangiectasia, pruritus, burning and dryness.

3. Global scores assessed by Investigator
Distributions of global scores are as follows:

		-4	-3	-2	-1	0	1	2	3	4	5	6	p
Week-2	Met qd	0	1	2	7	21	33	18	16	1	0	0	Met qd vs
	Veh qd	0	1	1	7	15	10	11	5	2	0	0	<u>Veh qd 0.46</u>
Week-4	Met qd	0	1	0	3	17	19	27	20	6	0	0	Met qd vs
	Veh qd	0	0	2	8	9	9	7	11	4	0	0	<u>Veh qd 0.32</u>
Week-7	Met qd	0	2	1	3	4	13	16	23	17	8	0	Met qd vs
	Veh qd	0	1	1	5	9	10	8	9	4	1	0	<u>Veh qd <0.01</u>
Week-10	Met qd	0	2	1	1	10	10	12	9	17	17	3	Met qd vs
	Veh qd	0	2	1	2	12	6	6	9	6	1	0	<u>Veh qd <0.01</u>
EP	Met qd	0	2	1	1	10	10	14	11	20	18	3	Met qd vs
	Veh qd	0	3	1	2	12	7	7	10	6	1	0	<u>Veh qd <0.01</u>

*EP=Endpoint, Met=metronidazole, Veh=vehicle. 6=Cleared: 100% improvement, 5=Excellent: 90-99% improvement, 4=Very good: 75-89% improvement, 3=Good: 50-74% improvement, 2=Fair: 25-49% improvement, 1=Slight: 1-24% improvement, 0=No change: no detectable improvement, -1=Slightly worse: 1 - 24% deterioration, -2=Mildly worse: 25-49% deterioration, -3=Moderately worse: 50-74% deterioration. -4=Severely worse: >75% deterioration.

Analyses of global scores with different levels of cutoff are shown below:

	Met qd	Vehicle qd	p values
Week-2	N=83	N=48	
≥25% improvement	18%	13%	0.47
≥50% improvement	1%	2%	1.00
≥75% improvement	0	0	-
Week-4	N=82	N=47	
≥25% improvement	27%	32%	0.55
≥50% improvement	6%	9%	0.72
≥75% improvement	0	0	-
Week-7	N=77	N=42	
≥25% improvement	53%	31%	0.02
≥50% improvement	31%	12%	0.02
≥75% improvement	10%	2%	0.16
Week-10			

(See under Primary Variables; week-10 & endpoint analyses gave same results)

*Met=metronidazole 1%.

Comments

1. Apart from data for ≥25% and ≥50% improvement at week-7, there was no significant differences between the treatment arms for success rates until week-10.
2. Between-group comparisons using "90% or greater improvement" or "cleared" have not been performed.
3. ANOVA was done using global scores as a continuous variable, with data from pooled centers and with Dr. Hino's and Dr. Stewart's sites excluded separately but not together. In all three situations analyzed, statistical significance was reached from week-7 to week-10/endpoint (p<0.01). However, analysis of the global distribution or with binary cutoff points to determine a "success rate" has not been presented with these centers excluded.

4. Patient's global evaluation scores at final visit

	Patient Numbers		p values
	Met* qd	Vehicle qd	
Final Visit	82(90)	45(49)	
Score 3	37(40)	10(12)	<0.01 (For distribution of scores)
Score 2	19(21)	9	
Score 1	12(14)	8	
Score 0	10(11)	12(13)	
Score -1	3	1(2)	
Score -2	1	2	
Score -3	0	3	
Score 1 or better	83%	60%	0.01

*Met=metronidazole 1%. Score 3=much better, 2=better, 1=somewhat better, 0=no change, -1=somewhat worse, -2=worse and -3=much worse. Patient numbers in endpoint analysis, if different from week-10 analysis, are given in parenthesis.

Comments

1. Patient's global showed significant differences between metronidazole and vehicle treatment at endpoint.
2. ANOVA (including Van Elteren's nonparametric test) and ANCOVA with baseline papule+pustule counts as covariate was done using patient's global scores at week-10/endpoint as a continuous variable, with data from pooled centers and with Dr. Hino's and Dr. Stewart's sites excluded separately but not together. In all situations analyzed, there was a significant difference between the treatment arms (p<0.01).

8.1.2.4.3 Safety Comparison

Adverse Events See Appendix 2. There were no deaths or serious adverse events. The majority of adverse events were mild and did not result in discontinuation of treatment. Discontinuations due to adverse events are shown above (8.1.2.4.1).

Laboratory Studies There were no samples taken for Clinical Laboratory studies.

Comment There were only two incidences where an adverse event was classified as treatment-related: rosacea worsened and acne.

8.1.2.5 Conclusions

1. At endpoint, metronidazole 1% cream qd was found to be superior to vehicle qd in the following primary parameters: percent reduction in papule counts, pustule counts, sum of papule and pustule counts and erythema scores and in Investigator's global. It was also superior to vehicle in secondary parameters including percent reduction in scaling/peeling, pruritus, overall rosacea score and patient's global.
2. Metronidazole 1% cream used in a qd regimen for the treatment of moderate to severe rosacea appears to be safe, with rare reports of treatment-related adverse events (rosacea worsened and acne).

8.1.3 Trial#3: Study#CMT 1286 Comparison of metronidazole 1% cream versus placebo in the treatment of rosacea

This was a study done in Canada comparing metronidazole 1% cream and placebo cream when used in a twice a day regimen in the treatment of rosacea. Since this study

did not address the requested indication of daily dosing for rosacea, its usefulness is primarily in demonstrating safety. This study has resulted in publication [A. Bitar, J. Bourguoin, N. Dore, R. Dubuc, J. M. Giroux, M. Landry, M.C. Roy and A. Mathieu-Serra. A double-blind randomized study of metronidazole (Flagyl®) 1% cream in the treatment of acne rosacea . A placebo-controlled study. *Drug Invest* 2 (4): 242-248, 1990], a copy of which was submitted in this Application. A review of this study is summarized here.

8.1.3.1 Objective/Rationale The objective was to evaluate the efficacy and safety of metronidazole 1% cream in the treatment of rosacea.

Comment The protocol was submitted in French without English translation. The study report, written in English, does not state the objective of this study.

8.1.3.2 Design Randomized, double-blind, placebo-controlled, multicenter study (7 centers) with two arms (metronidazole 1% cream and placebo cream), based on a 2x7 factorial model for parallel groups.

8.1.3.3 Protocol This study enrolled patients with rosacea aged 18 or over and having not more than 25 papulo-pustular lesions. It excluded patients in pregnancy or lactation, with alcohol or drug abuse, keratoconjunctivitis, conditions requiring anticoagulant, antibiotic, vasodilator or Antabuse therapy. The subjects were randomized to one of the two treatment groups (metronidazole or placebo) and examined at 3 visits: baseline, day-28 and day-56.

The test drug was applied twice daily, morning and evening, after face washing with soap and water. The medication was applied and rubbed gently into 0.25 cm² over each affected area to ensure absorption. It was consistently given over the course of study regardless of the degree of improvement. Evaluations included location and counts for papules and pustules, symptoms and signs including erythrosis (not actually defined, evaluated as present or absent and questions on frequency and precipitating factors were to be asked), erythema (scale of 0-5 with 0=normal and 5=severe erythema) and telangiectasia (scale of 0-4 with 0=none, 1=1 to 4, 2=5-10 and 3=>10) and global assessment by Investigator (1=no improvement, 2=minimal improvement, 3=good response and 4=marked improvement or complete remission) and by patient (1=marked improvement, 2=moderate improvement, 3=slight improvement, 4=no change, 5=slight worsening, 6=moderate worsening and 7=marked worsening). Safety parameters included adverse event incidence and laboratory data for hematology, chemistry and urinalysis.

Comment In contrast to the U.S. pivotal trials, (1) the application of test drug in this study was onto 0.25 cm² over each affected area instead of the whole face and (2) entry was restricted to subjects with up to 25 papulopustular lesions (8-50 in U.S. studies).

8.1.3.4 Results

8.1.3.4.1 Patient Disposition/Comparability

Seven centers (Bitar, Dore, Dubuc, Giroux, Landry, Roy and Mathieu-Serra) enrolled

100 subjects (50 per arm). All seven Investigators were from the Department of Dermatology, University of Montreal, Montreal, Quebec, Canada. The baseline characteristics of the two arms were similar for age, sex distribution, weight, height, baseline erythema ratings, papule count, pustule count, proportion of patients with erythrosis and previous treatment for rosacea. The metronidazole group had a shorter duration of illness (metronidazole vs vehicle=47 vs 59 months, p=0.02). The race distribution was not specified.

Comment All the centers were in one geographical area and in the same University. This may impact on the generalizability of the data.

Dropouts did not occur in the first month of the study. Eighteen discontinued in the second month:

	Metronidazole	Placebo
Lack of effect	2	3
Adverse event*	0	1
Intercurrent illness	2	1
Administrative	1	4
Lost to follow up	2	1
dosage violation	1	0
TOTAL	8	10

*One adverse event in the placebo group led to discontinuation: papulovesicular rash (#). Three cases of "intercurrent illness" not classified as "adverse events" also led to discontinuation - metronidazole: abscess (#) and psychosis (#); placebo: pharyngitis (#).

8.1.3.4.2 Efficacy Parameters

Comparison between treatment groups showed:

1. Erythrosis No significant differences at month-1 or month-2.
2. Location of rosacea No significant differences except for proportions of patients showing lesions on forehead at month-2 (metronidazole 8/19 and placebo 20/27; p<0.05) [nose, cheek and chin gave similar rates in the two groups].

3. Lesion counts (mean)		Metronidazole	Placebo	P
Papules	Baseline	8.1	8.9	NS
	month 1	4.5	6.5	<0.05
	month 2	3.2	6.4	<0.05
Pustules	Baseline	3.2	4.3	NS
	month 1	1.5	3.4	NS
	month 2	1.3	3.8	<0.05

4. Erythema scale No significant differences at month-1 or month-2.
5. Telangiectasia No significant differences at month-1 or month-2.
6. Global improvement No significant differences at month-1 or month-2 for Investigator's or patient's assessment.

8.1.3.4.3 Safety Comparison

Adverse Events The Applicant presented an analysis of adverse events excluding those unrelated to study medication:

		Metronidazole (N=50)	Placebo (N=50)
Local	Pruritus	3	2
	Pruritus+erythema	1	0
	Paresthesia	1	0
	Paresthesia+erythema	1	0
	Dry skin	1	0
	Burning	1	0
	Exfoliative dermatitis	0	1
	Papulovesicular eruption	0	1
	Oily skin	1	0
	Eye	Blurred vision	0
CNS	Headache	0	1
	Fatigue	1	0
	TOTAL	10	6

Comments

1. Some of the adverse events reported in the study are also symptoms in rosacea. Their actual significance and relationship to drug use is not clear.
2. One patient in the placebo group discontinued treatment because of adverse event (papulovesicular rash, # [redacted]). Adverse events not considered related to treatment were classified as "intercurrent illness"- metronidazole: abscess (# [redacted]), psychosis (# [redacted]) and placebo: pharyngitis (# [redacted]).

Laboratory Studies There were no significant abnormalities in Clinical Laboratory data (hematology, chemistry and urinalysis).

8.1.3.5 Conclusions

1. Metronidazole 1% cream bid was found to be effective in reducing papule and pustule counts upon treatment for 2 months for facial rosacea. However, neither patient's nor Investigator's global assessment demonstrated superiority for metronidazole 1% cream over placebo cream in a bid regimen.
2. Metronidazole 1% cream bid used in the treatment of facial rosacea appeared to be well tolerated.

8.1.4 Trial#4: Study#CMT 1487 Comparison of metronidazole 1% cream versus oral tetracycline in rosacea

This was a study done in Canada comparing metronidazole 1% cream bid and oral tetracycline tid in the treatment of rosacea. Since this study did not address the requested indication of daily dosing for rosacea, its usefulness is primarily in demonstrating safety. This study has resulted in publication [D. Schacter, R. K. Schacter, B. Long, N. Shiffman, R. Lester, S. Miller, H. Bargman, R. Haber and J. Bourgoquin. Comparison of metronidazole 1% cream versus oral tetracycline in patients with rosacea. *Drug Invest* 3 (4): 220-224, 1991], a copy of which was submitted in this Application. A review of this study is summarized here.

8.1.4.1 Objective/Rationale The objective was the comparison of efficacy and safety of metronidazole 1% cream with oral tetracycline in the treatment of

rosacea.

8.1.4.2 Design Randomized, double-blind, active-controlled, multi-investigator study with two arms (metronidazole 1% cream and oral tetracycline 250 mg tid) for a 2-month treatment period.

8.1.4.3 Protocol This study enrolled patients with rosacea aged over 18 and having papulo-pustular lesions over the face. It excluded patients in pregnancy or lactation, with anemia, thrombocytopenia, neutropenia or eosinophilia, allergy to metronidazole or tetracyclines, impaired liver or kidney function, keratoconjunctivitis and conditions requiring anticoagulant, vasodilator or disulfiram therapy. A washout period was given for prior antibiotic, vasodilator, or rosacea treatment: one month before entry. The subjects were randomized to one of the two treatment groups (metronidazole cream + placebo capsules or placebo cream + tetracycline capsules) and examined at 3 visits: baseline, day-28 and day-56.

The test cream (metronidazole or placebo) was applied twice daily, morning and evening, after washing of the face in the usual way the patient was used to and then drying. It was applied with finger tips and rubbed in lightly over 0.25 cm² to each affected area. It was consistently given over the 2 months of study. The oral capsule (tetracycline or placebo) was administered three times a day, one hour before or two hours after meal.

Comment In contrast to the U.S. pivotal trials but similar to CMT 1286, the application of test drug in this study was onto 0.25 cm² over each affected area instead of the whole face.

Water-based make up and use of the same skin cleanser throughout the study was allowed, while skin moisturizers were prohibited. Evaluations included counts for papules and pustules, clinical signs including erythema (scale of 0-5 with 0=normal and 5=severe erythema) and telangiectasia (scale of 0-4 with 0=none, 1=1 to 4, 2=5-10 and 3=>10) and global assessment by Investigator (1=no improvement, 2=minimal improvement, 3=good response and 4=marked improvement or complete remission) and by patient (1=marked improvement, 2=moderate improvement, 3=slight improvement, 4=no change, 5=slight worsening, 6=moderate worsening and 7=marked worsening). Safety parameters included adverse event incidence and laboratory data for hematology, chemistry and urinalysis.

8.1.4.4 Results

8.1.4.4.1 Patient Disposition/Comparability

Nine Investigators at 7 centers (Schachter, Schachter, Long, Lester, Haber, Taradash, Shiffman, Miller and Bargman) enrolled 125 subjects. All Investigators were from the Metropolitan Toronto area in Ontario, Canada. The baseline characteristics of the two arms were similar for age, sex distribution, weight, height, baseline erythema ratings, papule count, pustule count, degree of erythema or telangiectasia, proportion of patients with erythrosis and previous treatment for rosacea. The metronidazole group had a shorter duration of illness but this was considered to be not significant when

compared to the tetracycline group. The race distribution was not specified.

Comment All the centers were in one geographical area. This may impact on the generalizability of the data.

Patient disposition was as follows:

	Metronidazole	Tetracycline
Randomized	63	62
Dropped -		
Entry criteria violation	4	4
Lost to follow up	6	6
Administrative*	3	0
Intercurrent illness**	1	0
TOTAL excluded from analysis	14	10
Analyzed for Safety and Efficacy	49	52
Dropped -		
Adverse events†	5	3
Lack of efficacy	2	0
Intercurrent illness**	1	0
TOTAL early discontinuations	8	3

*Administrative dropouts: 3 cases in metronidazole arm - Lacking baseline laboratory data, interval between visits too long and noncompliance.

**Intercurrent illness included events considered to be unrelated to study drug, both being in metronidazole arm: "ear disorder" 1 & unspecified 1. As these were not classified as adverse events, CRFs were not submitted.

†Adverse event discontinuations were : metronidazole - contact dermatitis 3 (#s), GI upset 1 and papular rash 1 tetracycline - urticaria 1 dizziness/sweating 1 and GI upset 1

8.1.4.4.2 Efficacy Parameters

Comparison between treatment groups showed no significant differences in any efficacy parameter including erythrosis, location of rosacea, numbers of papules or pustules, erythema, telangiectasia and global improvement (Investigator's or patient's). For instance, the data on mean lesion counts are shown in the following Table:

		Metronidazole	Tetracycline	P
Papules	Baseline	18.4	21.0	NS
	month 1	9.9	9.7	NS
	month 2	6.2	5.0	NS
Pustules	Baseline	4.7	4.4	NS
	month 1	2.4	1.8	NS
	month 2	2.5	1.5	NS

However, there were significantly fewer papules or pustules at the month-1 or month-2 visits when compared to baseline values in both treatment groups ($p < 0.05$). Erythema and telangiectasia did not show significant changes in evaluations at month-1 or month-2 vs baseline for either arm. Both Investigator's global and patient's global indicated improvement by month-1 and further improvement by the end of month-2.

Comments

1. A formal analysis between the two treatments for bioequivalence using confidence intervals has not been presented.
2. Significance levels for additional improvement from month-1 to month-2 in global evaluation have not been given.
3. The value of comparison with baseline has limitations. In an active-controlled trial, it is difficult to be certain of the real efficacy of the active control in the

setting of the study. A result showing equivalence, therefore, does not necessarily establish efficacy. Baseline comparisons may be helpful if the natural history of the condition rarely gives spontaneous remission. Such comparison may be acceptable for rosacea.

8.1.4.4.3 Safety Comparison

Adverse Events The Applicant tabulated the patient numbers with adverse events related to treatment for the 101 patients analyzed:

	<u>Metronidazole (N=49)</u>	<u>Tetracycline (N=52)</u>
Gastrointestinal	7	6
GI upset	3	3
Nausea	2	1
Burping	1	0
Constipation	1	0
Abdominal cramps	1	0
Abdominal discomfort	0	1
Epigastric burning	0	1
Heartburn	0	1
Vomiting	0	1
Bloating	0	1
Dermatological	5	2
Photosensitivity	1	0
Vulvitis	1	0
Contact dermatitis	3	0
Folliculitis	0	1
Urticaria	0	1
Other	0	1
Dizziness	0	1
Sweating	0	1
TOTAL	12	9

Comments

- Adverse events not considered related to treatment were classified as "intercurrent illness". Two occurred in the metronidazole arm: "ear disorder" (#) and unspecified (#). CRFs have not been provided.
- Adverse events leading to discontinuation have been shown above (see footnote of Table in 8.1.14.1). It is unclear whether the discontinuation due to papular rash (described as "major nodular, papular and papulopustular lesion", patient#) was related to the rosacea itself or to treatment (metronidazole)
- Three cases of contact dermatitis occurred in the metronidazole arm and led to discontinuation of treatment. One patient (#) was labeled as having irritant contact dermatitis. Information on the other patients () was inadequate for identification of the nature of their contact dermatitis.

Laboratory Studies There were no significant abnormalities in Clinical Laboratory data (hematology, chemistry and urinalysis).

8.1.4.5 Conclusions

- This study had a high rate of dropout in each treatment arm (22/63 for metronidazole and 13/62 for tetracycline). This makes it difficult to be certain of conclusions drawn from the study for efficacy or safety.
- Metronidazole 1% cream bid was found to be as effective as tetracycline 250 mg tid in reducing papule and pustule counts upon treatment for 2 months for facial rosacea. Global improvement (Investigator's or patient's) was also comparable. However,

neither treatment provided significant improvement for erythema or telangiectasia after one to two months of therapy as compared to baseline.

3. Metronidazole 1% cream bid used in the treatment of facial rosacea appears to be well tolerated, although 3 cases of "contact dermatitis" were reported in the 63 patients so treated.

9. Overview of Efficacy

This NDA requests the indication of treatment of rosacea with a daily dosing regimen of metronidazole 1% cream. Two phase 3 trials done in the U.S. addressed this dosing regimen. In addition, two phase 3 studies done in Canada using a bid regimen have been presented. The Applicant also listed 16 publications from the literature in support of this application (see Section 7). These articles have not been submitted but discussed in the Integrated Summary of Efficacy. Only three of the 15 articles addressed daily dosing with a 1% metronidazole cream and they were all done in the same center and published in the same year (P. Gamborg Nielsen, 1983). One additional article studied metronidazole 1% cream but did not specify the dosing regimen.

Thus, support for the efficacy of a daily regimen of metronidazole cream in the treatment of rosacea comes from the following studies:

Pivotal trials - DL6027-9510 and DL6027-9516 &

Supporting studies - Nielsen. Br J Dermatol 108: 327, 1983; 109: 63, 1983 & 109: 122, 1983.

The other studies, including the two Canadian phase 3 trials (CMT 1286 and CMT 1487), may be useful in supporting safety but not efficacy for the indication being currently sought.

9.1 Dose-Ranging Studies

Dose-ranging studies have not been done. Instead, in one of the U.S. phase 3 trials (DL6027-9510), the efficacy of two dosing regimens (qd and bid) was studied and the effects of qd vs bid dosing were found to be not significantly different. Only two instances of significant differences were observed between qd and bid dosing in the reductions in clinical signs: scaling/peeling at week-2 ($p=0.03$) and telangiectases at week-4 ($p=0.02$) but not in the primary variables. Therefore, only the qd dosing regimen is being sought in this application.

9.2 Pivotal U.S. Trials

DL6027-9510 and DL6027-9516 were two studies having almost identical protocols apart from the elimination of two arms studying bid dosing (metronidazole and placebo cream) in DL6027-9516. They may be considered as adequate and well controlled studies to support this application because:

1. They have been adequately powered to include sufficient sample size;
2. They used vehicle cream as placebo control;
3. They were conducted by qualified Investigators;

4. They enrolled patients properly documented at baseline as having the condition to be treated and had them randomized to minimize bias and ensure comparability of treatment groups;
5. They used clinically relevant, well-defined and reliable outcome measures which were sensitive to the drug effect being studied (lesion counts and erythema) and
6. Their data have been subjected to statistical analysis which had been properly pre-planned.

Both were randomized, parallel-group, multicenter studies and properly blinded (double-blinded, and in DL6027-9510, with the addition of evaluator blinding for regimen), with protocols duly approved by IRBs and using the same formulation of metronidazole 1% cream, which is the subject of the current marketing application.

9.2.1 Enrollment and Demographic data in DL6027-9510 and DL6027-9516

Table 9.2.1A Enrollment and Evaluation for Efficacy in DL6027-9510 and DL6027-9516

Study	Met qd		Met bid	Veh qd		Veh bid	Total
	9510	9516	9510	9510	9516	9510	
Enrolled	97	104	98	50	52	48	
Total	201		98	102		48	449
Efficacy	92	89	92	49	50	44	
Total	181		92	99		44	416

*Met=metronidazole, Veh=vehicle.

Table 9.2.1B Baseline Demographic Data in DL6027-9510 and DL6027-9516

Study	Met qd		Met bid	Veh qd		Veh bid
	9510	9516	9510	9510	9516	9510
Pt number						
Sex						
M	31	32	41	13	14	11
F	61	57	51	36	36	33
Race						
W	90	88	91	48	45	43
B	0	1	1	0	2	0
H	2	0	0	1	3	1
Mean Age	49	49	51	49	47	50
Range						
Mean duration of rosacea (yr)	9.4	7.1	6.8	9.6	8.1	8.8
BL rosacea severity score	2.2	2.1	2.2	2.2	2.2	2.2

*Met=metronidazole, Veh=vehicle, BL=baseline, M=male, F=female, W=white, B=black and H=Hispanic.

Comments

1. Compared with other treatment groups in the same and in other studies, it is noted that in DL6027-9516, the metronidazole 1% arm excluded more subjects in Efficacy analysis (15%, vs up to 8% in other treatment groups). Most of these were dropouts who were noncompliant (use of antibiotics). However, the reasons for antibiotic use have not been provided in most of these patients.
2. Baseline characteristics of the treatment arms were similar in DL6027-9510, but in DL6027-9516, race and papule counts were significantly different between the metronidazole and placebo groups.

9.2.2 Primary Variables at Endpoint (Week-10) in DL6027-9510 and DL6027-9516

Because of the small number of pustules and the low proportion of patients actually having these lesion at baseline, their reduction in the metronidazole group at endpoint was not significant in DL6027-9510. In DL6027-9516, however, a significant treatment effect given by metronidazole was observed at endpoint/week-10 ($p \leq 0.02$). The following Table shows the mean change and percent reduction in counts or scores for the variables: papules+pustules, papules and erythema.

Table 9.2.2A Papules+Pustules, Papules and Erythema at Endpoint

Study	Met** qd		Met bid	Veh qd		Veh bid
	9510	9516	9510	9510	9516	9510
Pt number						
Papules+Pustules (mean)						
Change	-11*	-8*	-12*	-5	-3	-7
% reduction	58*	49*	58*	30	17	40
Papules (mean)						
Change	-10*	-6	-11*	-4	-4	-6
% reduction	55*	41*	59*	28	14	39
Erythema mean scores						
Change	-0.9*	-0.9*	-0.8	-0.4	-0.5	-0.6
% reduction	40*	42*	36	19	25	28

*Statistically significant ($p \leq 0.05$) between metronidazole and corresponding vehicle group.**Met=metronidazole, Veh=vehicle.

Investigator's Global was an additional primary variable. At endpoint, the success rates as defined by different cutoffs are shown in the following Table.

Table 9.2.2B Proportions of Patients showing Improvement above Certain Cutoff Points at Endpoint

Study	Met** qd		Met bid	Veh qd		Veh bid
	9510	9516	9510	9510	9516	9510
Pt number						
≥25% improvement	79%*	55%*	72%*	39%	36%	45%
≥50% improvement	51%*	44%*	51%	20%	16%	39%
≥75% improvement	22%*	25%*	34%	7%	2%	26%

*Statistically significant ($p \leq 0.05$) between metronidazole and corresponding vehicle group.**Met=metronidazole, Veh=vehicle.

Comment At endpoint, metronidazole 1% cream qd was superior to vehicle qd in the analysis of success rates using three different cutoffs (≥25%, ≥50% and ≥75% improvement) in the treatment for rosacea. However, between-group comparisons using "90% or greater improvement" or "cleared" have not been performed.

9.2.3 Evolution of Lesion Counts and Erythema during the Course of the Studies in DL6027-9510 and DL6027-9516

Table 9.2.3A Percent Reduction in Papules+Pustules, Papules and Erythema

Study	Met** qd		Met bid	Veh qd		Veh bid
	9510	9516	9510	9510	9516	9510
Papules+Pustules						
Baseline Count	19	15	19	17	18	16
%↓ at week 2	27	27*	21	16	8	14
%↓ at week 4	43*	35*	40	21	20	30
%↓ at week 7	51*	46*	48	26	15	28
%↓ at week10/Endpoint	58*	49*	58*	30	17	40
Papules						
Baseline Count	17	13	17	15	15	15
%↓ at week 2	26	25	20	17	9	9
%↓ at week 4	41*	30	40	25	14	29
%↓ at week 7	50*	40*	47	26	8	28
%↓ at week10/Endpoint	55*	41*	59*	28	14	39
Erythema scores						
Baseline Score	2.3	2.2	2.2	2.2	2.2	2.2
%↓ at week 2	17*	18	14	4	11	10
%↓ at week 4	27*	26	25	10	24	18
%↓ at week 7	33*	35	33	10	27	28
%↓ at week10/Endpoint	40*	42*	36*	19	25	28

*Statistically significant ($p \leq 0.05$) between metronidazole and corresponding vehicle group. **Met=metronidazole, Veh=vehicle. Week-10 and endpoint gave identical results.

Table 9.2.3B Proportions of Patients showing Global Improvement above Specific Cutoff Points

Study	Met** qd		Met bid	Veh qd		Veh bid
	9510	9516	9510	9510	9516	9510
Week-2 Pt. No.						
≥25% improvement	35%	18%	34%	19%	13%	19%
≥50% improvement	8%	1%	12%	9%	2%	10%
≥75% improvement	3%	0%	4%	0%	0%	2%
Week-4 Pt. No.						
≥25% improvement	60%*	27%	56%	26%	32%	44%
≥50% improvement	26%	6%	36%*	12%	9%	15%
≥75% improvement	10%*	0%	14%	0%	0%	5%
Week-7 Pt. No.						
≥25% improvement	68%*	53%	62%	38%	31%	50%
≥50% improvement	39%*	31%*	46%	21%	12%	33%
≥75% improvement	20%	10%*	26%	10%	2%	14%

*Statistically significant ($p \leq 0.05$) between metronidazole and corresponding vehicle group. **Met=metronidazole, Veh=vehicle. Week-10 data not included here (see Table 9.2.2B).

9.2.4 Secondary Variables: Patient's Global, Overall Rosacea Scores and Clinical Signs/Symptoms for DL6027-9510 and DL6027-9516

Patients evaluated the study at the final visit and found the test medication providing at least "somewhat better" improvement in the majority of instances.

Table 9.2.4A Proportions of Patients showing Improvement as assessed by Patient's Global

Study	Patient Numbers				Paired Comparisons (p values)	
	Met* qd	Met bid	Vehicle qd	Vehicle bid	Met qd vs Veh qd	Met bid vs Veh bid
Study 9510	N=82	N=79	N=41	N=38		
Score 1 or better	82%	78%	61%	58%	0.02	0.03
Study 9516	N=82		N=45			
Score 1 or better	83%		60%		0.01	

*Met=metronidazole, Veh=vehicle. Score 3=much better, 2=better, 1=somewhat better, 0=no change, -1=somewhat worse, -2=worse and -3=much worse.

Comment Analysis using a higher score as cutoff has not been presented.

For the daily regimen with metronidazole 1% cream, overall rosacea scores indicated its superiority over vehicle cream at endpoint in both studies, and in one study, DL6027-9510, superiority was achieved as early as week-4. Metronidazole 1% cream bid was not better than vehicle bid, as there was considerable vehicle effect. Clinical signs and symptoms gave variable results and the endpoint data are shown in the following Table.

Table 9.2.4B Percent Reductions in Overall Rosacea Scores and Clinical Sign/Symptom Scores at Week-10/Endpoint

Study	Met** qd		Met bid	Veh qd		Veh bid
	9510	9516	9510	9510	9516	9510
Overall Severity Score	N= 82	80	79	41	45	38
%↓	39*	38*	39	19	18	30
Burning	N= 29	20	28	10	10	13
%↓	84	86	89	64	88	92
Dryness	N= 41	50	39	21	24	22
%↓	78	65	60	57	64	69
Scaling/Peeling	N= 39	44	36	18	16	19
%↓	84*	77	45	36	66	76
Pruritus	N= 32	28	34	16	11	13
%↓	80	98*	86*	54	64	35
Telangiectases	N= 75	79	74	37	44	35
%↓	8*	4	13	+5	10	7

*Statistically significant ($p \leq 0.05$) between metronidazole and corresponding vehicle group. **Met=metronidazole, Veh=vehicle.

9.2.5 Metronidazole 1% Cream QD vs BID Dosage Regimens in DL6027-9510
See Section 9.1.

9.3 Supportive Studies with Metronidazole 1% Cream QD Dosing Regimen

Findings from 3 studies from one center in Sweden were presented:

Study 1 - P. Gamborg Nielsen. Br J Dermatol 108: 327, 1983

Study 2 - P. Gamborg Nielsen. Br J Dermatol 109: 63, 1983

Study 3 - P. Gamborg Nielsen. Br J Dermatol 109: 122, 1983

The Applicant has not submitted the original articles in the Clinical Section of this NDA. The following account is derived from the description given by the Applicant. All three studies included a qd regimen of metronidazole in parallel with a second arm using another therapy for the treatment of rosacea.

Table 9.3 Findings in Gamborg Nielsen's Studies with Metronidazole 1% Cream QD

<u>Study</u>	<u>Treatment</u>	<u>Findings</u>		
1 (N=81)	Met 1% cream qd x 2 mo placebo cream qd x 2 mo	<u>≥50% improvement</u> 65%* after 1 mo; 60%* after 2 mo 27% after 1 mo; 22% after 2 mo		<u>Lesion Counts and Erythema</u> Significant ↓ vs placebo, esp in 1st mo
2 (N=51)	Met 1% cream qd x 2 mo Oxytetracycline 250 mg bid x 2 mo	<u>Clinical improvement</u> 96% 96%	<u>Photographic improvement</u> 84% 91%	<u>Self-assessed improvement</u> 88% 91%
3 (N=33)	Met 1% cream qd x 4 mo Met 1% cream qod x 4 mo	This is an open label study enrolling 33 new patients (16 qd and 17 qod) treated for 4 mo with Met 1% cream. They were then put to a 6 mo no-treatment follow up to see relapse rates. Result showed that 50% of patients had no relapse regardless of qd or bid dosing. This was contrasted with subjects in Study 1 & Study 2 who were followed up for 6 mo after 2 mo of met or oxytetracycline: 30% (met) and 15% (oxytetracycline) had no relapse.		

*Figures showing significant differences with placebo cream are preceded by asterisk. Met=metronidazole.

Comments

1. The original articles should be submitted for review.
2. In Study 1, qd dosing with metronidazole 1% cream was successful in lesion count and erythema reduction as well as in global, using a 50% improvement cutoff.
3. In Study 2, the only information given refers to any improvement, as assessed by physician, photographs and patient. No analysis for bioequivalence is presented.
3. In Study 3, the authors claimed that treatment for 4 months was associated with a lower rate of relapse than treatment for 2 months, regardless of qd or qod dosing. However, this is a comparison across studies, the validity of which is questionable. In addition, significance levels using survival analysis have not been presented. In this application, the Applicant states that well controlled trials have not confirmed the superiority of a 4-month treatment regime (p. 24-74). However, these well controlled studies have not been listed or presented.

9.4 Supportive Studies with Metronidazole 1% Cream BID Dosing Regimens

9.4.1 Studies using Dermik's Metronidazole 1% Cream

Study reports of two Canadian studies using the same formulation as Dermik's metronidazole 1% cream were submitted:

CMT 1286: vehicle-controlled study with 100 patients treated for 2 months

CMT 1487: active-controlled study (tetracycline 250 mg tid) with 100 patients treated for 2 months.

In the vehicle-controlled study, metronidazole 1% cream bid was superior to vehicle bid on counts for papules and pustules at the end of two months of treatment. For the tetracycline-controlled study, metronidazole 1% cream was found to be as effective as tetracycline 250 mg po tid on papule and pustule count and global improvement by physicians and patients (note: no formal analysis for bioequivalence with confidence intervals presented). Clinical signs and symptoms including erythrosis, erythema and telangiectasia did not show significant changes vs baseline in either study.

Table 9.4.1 Efficacy Parameters at Endpoint (Month-2) for CMT 1286 & CMT 1487

	CMT 1286		CMT 1487	
	Met	Veh	Met	Tetracycline
Mean no of papules				
Baseline	8.1	8.9	18.4	21.0
Month 1	4.5*	6.5	9.9	9.7
Month 2	3.2*	6.4	6.2	5.0
Mean no of pustules				
Baseline	3.2	4.3	4.7	4.4
Month 1	1.5	3.4	2.4	1.8
Month 2	1.3*	3.8	2.5	1.5
Global improvement**				
Month 1	2.8 (70%)*	3.3 (38%)	2.3	2.2
Month 2	2.5 (88%)	3.2 (68%)	2.1	1.7
Patient's assessment **				
Month 1	2.1	2.0	2.5	2.6
Month 2	2.5	2.1	3.1	3.1

*Significant difference vs vehicle (p<0.05).

*Proportion of patients who showed any improvement vs baseline given in parentheses.

**scored as 1= very much improved, 2=much improved, 3=minimal improvement, 4=no change, 5=minimally worse, 6=much worse and 7=very much worse

**scored as 1=no change or deterioration, 2=minimal improvement, 3=good response and 4=marked improvement.

Comments

1. These two studies demonstrate that metronidazole 1% cream bid is effective in reducing papular and pustular counts in rosacea. They have not shown efficacy in relation to the clinical signs/symptoms including erythema and erythrosis, although both physician and patient assessments suggest a trend towards effectiveness.
2. These studies used a higher dosing regimen (bid) and cannot support efficacy for the current request for a lower dosing regimen (qd).

9.4.2 Other Studies with Metronidazole 1% Cream BID for Rosacea

Two studies which used twice daily metronidazole 1% cream in the treatment of rosacea have been published: Bjerke et al, 1989 and Eriksson and Nord, 1987 (see Section 7 for design of these studies). These articles have not been submitted. The Applicant gave their findings as follows:

Bjerke's Study Metronidazole 1% cream (51 patients) was compared to vehicle (50 patients) for a 2-month treatment course. At week-8, 97 subjects were evaluable:

	Metronidazole	Vehicle
Reduction in Papule+Pustule count	78%	48%
Global (improved/unchanged/worse)	88%/12%/0	55%/36%/9%

Eriksson and Nord Study This is an uncontrolled study with 6 men and 14 women having metronidazole 1% cream applied for one month in the treatment of rosacea. Results were - (1) significant reduction in the number of plaques and pustules; (2) improvement in 16/20 patients by physician's assessment and 19/20 by patient assessment; and (3) reduction in the number of lesions containing staphylococci and propionibacteria but strains present were resistant to metronidazole(>1 mg/ml) in culture.

Comment Bjerke's study did not contain sufficient details and Eriksson and Nord's

study was uncontrolled. Moreover, they used a bid dosing regimen which cannot support the current application for a qd regimen.

9.5 Other Studies with Metronidazole in the Treatment of Rosacea

Out of the 11 remaining published studies involving metronidazole in the treatment of rosacea and presented by the Applicant, one used a 1% cream without specifying dosing regimen, 5 used other metronidazole topical formulations and 5 used oral dosing. The studies are:

Table 9.5 Other Studies with Metronidazole in the Treatment of Rosacea

Study	Publication	Met*	Control	Pt no/Tx Duration
Topical metronidazole				
1	Veien VK <i>et al Cutis</i> 1986; 38: 209-210	1% cr	tetracycline po	/2 mo
2	Aronson IK <i>et al Drug Intell Clin Pharm</i> 1987; 21: 346-351	3% gel	vehicle	/9 wk
3	Aitken G <i>Presse Med</i> 1983; 12: 1490-1491	5% cr	chlortetracycline po	/3 mo
4	Dupont C <i>Br J Dermatol</i> 1984; 111: 499-502	5% susp	none	/3 mo
5	Bleicher PA <i>et al Arch Dermatol</i> 1987; 123: 609-614	3% gel	vehicle	/9 wk
6	Lowe NJ <i>et al Cutis</i> 1989; 43: 283-286	3% gel	none	/8 wk
Oral metronidazole				
7	Pye RJ, Burton JH <i>Lancet</i> 1976; 1: 1211-1212	200mgbid oral	placebo	/6 wk
8	Kurkcuoglu N Atakan N <i>Arch Dermatol</i> 1984; 120:837	250mgbid	none	/3 wk
9	Saihan EM, Burton JL <i>Br J Dermatol</i> 1980; 102: 443-445	200mgbid	oxytetracycline po	/12 wk
10	Nasir MA <i>JPMA</i> 1985; 35: 148-149	200mgbid	tetracycline po	/8 wk
11	Guilhhou JJ <i>et al Ann Dermatol Venereol</i> 1979; 106: 127-129	250mg q2d to 250mgbid	none	/2-6 mo

*Met=metronidazole, Pt No=patient number, cr=cream, susp=suspension and Tx duration=treatment duration

Their findings are shown in the following Tables.

Table 9.5A Findings in Other Studies with Topical Metronidazole in the Treatment of Rosacea

Study	Finding
1	%↓ erythema: <u>Met</u> 11% & <u>tetra</u> 13%, but earlier onset of action by <u>tetra</u> . Clearing of lesions in more <u>tetra</u> pts*
2	Patients having "Improvement" at wk-3, 6, 9 & 3wks posttreatment: 51%, 60%, 67% & 55% with <u>Met</u> 4%, 8%, 12% & 4% with <u>Veh</u> . Global more favorable for <u>Met</u> at all evaluations*. Erythema ↓ with <u>Met</u> & <u>Veh</u> but more with <u>Met</u> .
3	At endpoint (3 mo): "Improvement": 68% with <u>Met</u> , 82% with <u>chlortet</u> & 40% with <u>placebo</u> .
4	Uncontrolled study: 73% pts "marked" reduction in papules & some Erythema ↓.
5	Lesion ↓: up to 65% with <u>Met</u> & a mean of 15% with <u>placebo</u> . Posttreatment (3 wk without <u>Met</u>), lesions ↑. %↓ erythema: "less marked".
6	Uncontrolled study on severe/recalcitrant rosacea: ↓ erythema: 84%. Lesion counts & global improved.

*indicates parameter showing statistically significant difference between treatments.

Met=metronidazole, Veh=vehicle, tetra=tetracycline, chlortet=chlortetracycline; study numbers refer to studies in Table 9.5.

Table 9.5B Findings in Studies with Oral Metronidazole in the Treatment of Rosacea

Study	Finding
7	↓ erythema* and lesion counts* (esp. papules & pustules): <u>Met</u> superior to <u>placebo</u> .
8	Uncontrolled study on pts refractory to tetra or triamcinolone: ↓ erythema and lesion counts in 10-21 days.
9	Global at wk-6 & -12: <u>Met</u> and <u>oxytet</u> both gave "significant improvement" but no "significant differences" between treatment groups.
10	Controlled, unblinded study: patients with complete Lesion clearing at end of 8 wks: <u>Met</u> 56% & <u>tetra</u> 60%.
11	Uncontrolled study: Within 2 mo, Global "marked improvement"=90%, & "fair" + "none" =8% of patients.

*indicates parameter showing statistically significant difference between treatments.

Met=metronidazole, Veh=vehicle, tetra=tetracycline, oxytet=oxytetracycline; study numbers refer to studies in Table 9.5.

Comment These 11 studies support the effectiveness of metronidazole in the treatment of rosacea. However, because of the lack of complete documentation, differences in dosage form and dosing regimen and the nature of some of these studies (4 uncontrolled and 1 open studies), their usefulness in support of the current application is limited.

9.6 Subset Analysis

Subset analyses for age, sex and race have not been performed for efficacy.

Comment Although these are posthoc analyses not powered to support efficacy, they are required in order to examine trends and generate new hypotheses for further exploration.

9.7 Conclusions

1. The two phase 3 U.S. trials DL6027-9510 and DL6027-9516 appear to be successful studies in establishing the efficacy of daily metronidazole 1% cream in the treatment of rosacea and may be considered pivotal. The two Canadian studies and the 16 reports in the literature add little to support the current application for a daily dosing regimen for metronidazole 1% cream in the treatment of rosacea.
2. With a 10-week course of treatment, daily administration of metronidazole 1% cream was effective in the treatment of facial rosacea as evaluated by the primary parameters: percent reduction of (a) erythema, (b) papules, and (c) papules plus pustules and (d) Investigator's global assessment, both by distribution and by arbitrary dichotomous cutoffs for the degree of improvement. In addition, one of the two U.S. trials showed success in percent reduction of pustule counts.

10 Overview of Safety

Metronidazole is currently available in several dosage forms, including those for systemic (oral and intravenous) and topical (gel and vaginal cream) administration. For the approved indications of i.v. metronidazole with recommended doses of 2-2.5 Gm/d (29-36 mg/kg/d) and those of oral metronidazole with recommended doses of approximately 30 mg/kg/d, exposure far exceeds that from metronidazole 1% cream

used to treat facial rosacea, because of the very low absorption through skin (see PK studies in Section 10.1.9) and the limited area to be treated. Indeed, an oral dose of metronidazole 200 mg/d may yield a C_{max} of 4-7 mg/ml, two orders of magnitude higher than the plasma levels found in those patients with detectable metronidazole (up to 45 ng/ml; 10 out of 40 patients) after one month of daily application of metronidazole 1% cream (P. Gamborg Nielsen, see Section 10.1.9).

10.1 Background and Methodology for Safety Review

Although metronidazole is available in other dosage forms, the indications and expected amount of patient exposure are very different from those for metronidazole 1% cream in the treatment of rosacea. As *skin* exposure for facial application is limited (assuming 2% of an adult's body surface area of 1.7 m², amount used=6.8 mg/d) and percutaneous absorption is minimal, *systemic* exposure is probably insignificant. It would be more appropriate to focus on the safety data from studies involving treatment of rosacea with topical metronidazole, especially those with the current formulation proposed for marketing.

This review is based on data submitted on the two pivotal studies DL6027-9510 and DL6027-9516, the two Canadian studies CMT 1286 and CMT 1487 and 16 published studies, together with six clinical pharmacology studies (3 PK studies: ICP#63/0001, ICP#63/0003 and DL6027-9520 and 4 dermal safety studies: ICP#63/0001, DL6027-9511, DL6027-9517 and DL6027-9518). These clinical pharmacology studies are discussed in Section 10.1.9. The 16 supportive published studies provided scant and incomplete safety data for an adequate review and five of these studies used oral metronidazole. The safety data of these supportive studies were reviewed whenever possible.

The numbers of healthy subjects or patients included in studies with the use of the current formulation of metronidazole 1% cream are:

<u>Phase 1</u>	<u>Metronidazole Vehicle</u>		<u>Phase 3</u>	<u>Metronidazole Vehicle</u>	
DL6027-9511	258	258	DL6027-9510	195	98
DL6027-9517	21	21	DL6027-9516	103	52
DL6027-9518	29	29	CMT 1286*	50	50
DL6027-9520	<u>16</u>	<u>0</u>	CMT 1487*	<u>49</u>	<u>52</u>
TOTAL	324	308		397	252
GRAND TOTAL: Metronidazole/Vehicle=721/560					

*The Applicant has not confirmed that these two studies definitely used current formulation

The methodology of review is analysis of (1) adverse events data and (2) laboratory findings, if available. Exposure in the four phase 1 studies was rather limited, and the dermal safety studies were designed to elicit adverse reactions. Thus, the database for adverse events in this review primarily involves the two U.S. phase 3 trials, supplemented by the two Canadian studies.

Baseline Characteristics of the populations are given below:

	U.S. Studies DL6027-9510 & DL6027-9516				Canadian Studies CMT 1286 & 1487		
	Met qd	Met bid	Veh qd	Veh bid	Met bid	Veh bid	Tetracycline tid
	N=200	N=98	N=102	N=48	N=99	N=50	N=52
Sex M	70	44	27	12	42	19	20
F	130	54	75	36	57	31	32
Race White	197	97	96	47	Information on race N/A		
Black	1	1	2	0			
Hispanic	2	0	4	1			
Mean age	49	51	48	50	46-50**	51	45
Mean rosacea duration (yr)	8	7	9	9	4	5	5
BL severity	2.2	2.2	2.2	2.2	Information on BL severity N/A		
BL no of papules	15	17	15	15	8-18**	9	21
BL no of pustules	2	2	3	2	3-5**	4	4

*Met=metronidazole, Veh=vehicle, BL=baseline, N/A=not available. **Figures are mean values in each study.

Extent of exposure to metronidazole 1% cream or control was as follows:

U.S. Studies	Met* qd	Met bid	Veh qd	Veh bid	Canadian Studies	Met bid	Veh bid	Tetracycline tid
Tx Days	N=200	N=98	N=102	N=48	Tx Months	N=99	N=50	N=52
64-70	96	52	48	22	2	83	50	49
≥70	81	37	45	18				

*Met=metronidazole, Veh=vehicle, Tx=treatment

10.1.1 Deaths

One patient died during study DL6027-9510. The patient had a history of atherosclerotic heart disease and hypertension since 1956 and diabetes since 1987. Myocardial infarction occurred 35 days after start of treatment. This event and the death was considered to be not related to treatment.

10.1.2 Dropouts

10.1.2.1 Overall Pattern of Dropouts

	U.S. Studies DL6027-9510 & DL6027-9516				Canadian Studies CMT 1286 & 1487		
	Met qd	Met bid	Veh qd	Veh bid	Met bid	Veh bid or Tetracycline tid	
	N=200	N=98	N=102	N=48	N=99	N=102	
Non-compliance	16	3	3	3	Dosage violation	1	0
Treatment failure	1	2	2	2	Lack of effect	4	3
Adverse event	3 (death 1)	2	1	2	Adverse event	5	4
					Intercurrent illness	3	1
Did not wish to continue	1	1	1	1	Administrative	1	4
Lost to follow up	3	0	1	0	Lost to follow up	2	1
TOTAL	24	8	8	8		16	13

*Met=metronidazole 1%, Veh=vehicle.

Comments

1. The U.S. studies had 8-12% dropout rates for metronidazole regimens and 8-17% dropout with vehicle, while the Canadian studies had 16% dropout for metronidazole bid and 13% for controls. Terminations due to adverse events were 13% and 25% of total dropouts for the qd and bid regimens respectively in the U.S. studies. In the Canadian studies, only bid regimen was used and the termination rate for adverse events was about 30% of dropouts for both metronidazole and for controls.

2. Noncompliance was a major cause of dropouts in the U.S. studies (38-67% of dropouts) and the Applicant attributed this to the use of antibiotics. However,

details of the illnesses necessitating antibiotic use have not been presented in most instances. Moreover, there is disparity in the distribution of this type of noncompliance, as the metronidazole 1% cream qd regimen had most of the dropouts due to this category. For the Canadian studies, this did not appear to have been a problem.

10.1.2.2 Adverse Events Associated with Dropout

<u>Study/Regimen</u>	<u>Adverse Events leading to Termination</u>
DL6027-9510	
Metronidazole 1% bid:	contact dermatitis of face (#); burning (#)
Vehicle qd:	burning (#)
Vehicle bid:	contact dermatitis (site unspecified) (#); redness, burning & rosacea exacerbation (#)
DL6027-9516	
Metronidazole 1% qd:	comedonal acne flare (#), exacerbation of rosacea (#) and death from myocardial infarction (#)
CMT 1286	
Vehicle bid:	papulovesicular rash (#)
CMT 1487	
Metronidazole 1% bid:	contact dermatitis (#s, GI upset and papular rash
Tetracycline	urticaria 1, dizziness/sweating and GI upset

*considered unrelated to treatment

Comment: Adverse events associated with use of metronidazole 1% cream or vehicle that led to discontinuation were essentially due to local effects. Only two cases involved nondermatological events and both were unlikely to be related to treatment.

10.1.3 Other Serious Adverse Events

There were no other serious adverse events in the U.S. studies. In the Canadian studies, the Applicant stated there were no deaths and no serious and unexpected adverse events, despite a case of psychotic reaction in CMT 1286 (#).

10.1.4 Other Search Strategies not applicable

10.1.5 Adverse Event Incidence Tables

The two U.S. and two Canadian phase 3 trials (DL6027-9510, DL6027-9516, CMT 1286 and CMT 1487) were similar in design and used similar formulations of metronidazole 1% cream. The treatment periods were 2 months to 10 weeks. The patients had similar age and sex distribution. However, some differences exist:

1. The Canadian studies had patients with shorter duration of rosacea (mean 4-5 years ; U.S. studies 7-9 years) and the mean baseline papule counts in the two Canadian studies differed by a factor of >2 (CMT 1286=8-9, CMT 1487=18-21; U.S. studies=15-17).
2. The U.S. study, DL6027-9516, only compared the qd regimens of metronidazole and placebo, while the Canadian studies only used the bid regimen of metronidazole to compare with placebo (CMT 1286) and with active control (tetracycline, CMT 1487).
3. Entry restriction on the basis of baseline counts for papulopustular lesions differed: 8-50 for the U.S. trials, ≤25 for CMT 1286 and no restriction for CMT 1487.

Despite these differences, it is possible to examine the combined data by keeping the dosage regimens distinct. Adverse event information from the pooled database

containing these two U.S. and two Canadian studies (excepting those in the tetracycline group in CMT 1487) is shown in Appendix 3. Most adverse events were mild or moderate in severity. Only two adverse events were classified as "severe" and related to treatment:

<u>Study</u>	<u>Patient no</u>	<u>Event</u>
DL6027-9510		"Application site reaction": severe burning, which was present at baseline
DL6027-9516		Flare of comedonal acne from day 8; stopped treatment on day 14

Adverse event information from the 16 published studies is not in sufficient detail to permit a full analysis. Indeed, in nine of the studies, the authors mentioned that there were no adverse events. The information in the seven studies that had relevant data is shown in the following Table:

<u>Author</u>	<u>Drug</u>	<u>N</u>	<u>Adverse Event</u>	<u>No. with AE</u>	<u>No. who discontinued</u>
Aitken	Metronidazole 5% cream	23	Not specified	3	0
	Chlortetracycline	25	Not specified	-	0
	Placebo	25	Not specified	3	0
Veien	Metronidazole 1% cream	37	Dermatologic	7	-
	Tetracycline	39	Dermatologic	11	-
Bjerke	Metronidazole 1% cream	50	Minor irritation	1	0
	Placebo cream	47	erythema & pain	1	1
Bleicher	Metronidazole 0.75% gel	40	Eyes tear	1	0
	Placebo	40	-	-	-
Lowe	Metronidazole 0.75% gel	19	Skin irritation	1	0
Pye	Metronidazole 200 mg p.o. bid	15	Headache	1	1
			Furred tongue	1	0
	Placebo	14	Headache	1	1
Guilhou	Metronidazole 250 mg p.o. q2d to bid	62	GI upset	6	2

More detailed comments are given below (Section 10.2)

10.1.5.1 Additional Analyses and Explorations

As there were approximately twice as many females as males studied, the Applicant performed a subset analysis on adverse event data based on gender. This posthoc analysis did not show any meaningful differences in incidences between the two sexes. Age and race were not explored.

Although systemically administered metronidazole may show interaction effects with concomitant warfarin, alcohol, disulfiram and drugs that induce liver microsomal enzymes, drug-drug interactions are not known with topical metronidazole. There is no evidence either in the efficacy or in the adverse event data to suggest such interactions occurred with use of metronidazole 1% cream.

Drug-disease interactions are not explored. The studies were designed to examine the effect of metronidazole on subjects who were healthy other than having rosacea.

10.1.6 Laboratory Findings

As metronidazole is a well studied and marketed drug, no clinical laboratory data were collected in the U.S. development program. The two supportive Canadian studies (CMT 1286 and CMT 1487) which used a higher dosing regimen (bid) than the one requested in this NDA (qd) found no consistent clinically significant abnormalities. In addition, in the PK studies DL6027-9520 and ICP#63/0003 and throughout the skin irritation study ICP#63/0001, hematology, blood chemistry and urinalysis data showed no consistent significant abnormalities.

10.1.7 Vital Signs

No evidence of vital sign changes associated with use of metronidazole 1% cream.

10.1.8 ECGs Not studied.

10.1.9 Special Studies

Three studies on the pharmacokinetics of metronidazole 1% cream and four dermal safety studies were performed by the Applicant. In addition, two published studies with PK data were used for support of this application. One PK study, DL6027-9520, and 3 dermal safety studies DL6027-9511, DL6027-9517 and DL6027-9518 used the current Dermik formulation which is the subject of this application for marketing.

10.1.9.1 Pharmacokinetic Studies These studies have been reviewed by Biopharm. Only a summary of the results and safety findings will be given here.

10.1.9.1.1 Study DL-6027-9620 Single-Dose Pharmacokinetics of Topical Metronidazole 1% Cream in Normal Adults

This study was done at _____ in 1996, and used the current formulation to determine absorption and pharmacokinetic parameters up to 24 hr after a single open application of a 1 Gm dose of the cream to the face (225 cm²) in normal adults. Treated areas were not washed for at least 12 hr.

Among the 16 subjects enrolled, there were 8 males and 8 females. Fourteen were Caucasian and 2 Hispanic. Mean age was 28.4 (range _____). All plasma levels for metronidazole were below 100 ng/ml. One subject had two mild adverse events (nausea and diarrhea), Clinical laboratory tests (hemoglobin, serum chemistry and urinalysis) were normal at screening and at day-2.

10.1.9.1.2 Study ICP#63/0003 Skin Penetration and Percutaneous Absorption of Metronidazole Following Topical Application to Healthy Volunteers

This investigation was done by Darragh *et al* at the Institute of Clinical Pharmacology, Dublin, Ireland in 1985. Radiolabeled ¹⁴C-metronidazole cream 2% was applied (100 mg) and left in place in the upper back for 12 hr (to intact skin of 8 subjects and stripped skin of another 8). There were 16 male subjects (aged 20-45). Recovery of radioactivity

(up to 144 hr after application) is shown in the following Table:

		<u>Mean±SD as % dose applied</u>	
		<u>Intact skin</u>	<u>Stripped skin*</u>
Skin	Q-tips	94.3±3.3	93.2±6.9
	Strippings	1.0±0.8	0.4±0.3
Urine		1.3±0.7	3.4±5.4 (1.4±0.9)**
Plasma		Undetectable	Undetectable**
Feces		0.1±0.2	0.6±1.2 (0.2±0.2)**
Total		96.6±2.8	97.6±2.4

*Subject ● excluded from analysis: unacceptably low recovery (total radioactivity recovered 37%).

**Subject ● had detectable plasma levels up to 36 hr after application (C_{max} 5.5-5.7 ng Eq metronidazole at 6-12 hr). Urine and fecal recovery after exclusion of this subject's data shown in parenthesis.

The following adverse events were reported: headache 1, diarrhea 1 and abrasion of treatment area due to stripping 2 (Subjects 1 and 4). Clinical laboratory results (hematology, serum chemistry and urinalysis) were unremarkable.

Comment Subject ● who had abrasion of the treatment area with stripping gave detectable plasma levels of metronidazole (see above Table) and had high urine and fecal excretion of metronidazole (15.6% and 3.4% recovery of applied dose respectively). This underscores the differences in absorption between intact and nonintact skin, which may have relevance in actual clinical usage.

10.1.9.1.3 Study ICP#63/0001 A Forty-four Day Cumulative Irritancy Evaluation of Three Topical Metronidazole Formulations

This investigation was also done by Darragh *et al* at the Institute of Clinical Pharmacology, Dublin, Ireland in 1986 on healthy volunteers. It was essentially a cumulative irritancy/phototoxicity test (see below) but also measured plasma metronidazole levels. Six application sites on the back were used: to intact skin, 3 concentrations of metronidazole cream (0.5%, 1% and 2%) and placebo cream were applied for 24 hr; and to stripped skin (stripped ten times with scotch tape), metronidazole cream 2% and placebo cream were applied for 24 hr. Quantity applied was 200 mg of material per site. Upon removal of test materials and evaluation of the application sites by a blinded observer, the whole procedure was repeated. This was done daily (Monday through Friday; weekend patches left for 72 hr) for a period of 6 weeks, with the last patch applied on day-43 and removed on day-44. Plasma metronidazole levels were measured on day-44 samples.

Twenty-four Caucasian subjects enrolled: males 7 and females 17, with age range . Six had undetectable plasma levels (detection limit=20 ng/ml) and the remaining 18 gave a mean level of 31 ng/ml (range ng/ml) on the day-44 sample.

Apart from local reactions (see 10.1.9.2.4) adverse events included: vomiting/diarrhea 1, sore throat 1, lower abdominal cramp 1 and hand rash 1. Serum chemistry and urinalysis data were unremarkable throughout the study. Compared with prestudy values, there was a significant reduction in WBC count on days -24, -36 and -44 (mean values of 6.0, 6.0 and 5.8 respectively vs baseline of 6.9 and poststudy follow-up level of 6.4 seven days after last patch removal) but these did not show correlation with

plasma metronidazole levels and were not considered drug-related.

10.1.9.1.4 Publication: P. Gamborg Nielsen. Br J Dermatol 1983; 108: 327-332. Treatment of Rosacea with 1% Metronidazole Cream. A Double-blind Study

10.1.9.1.5 Publication: Aronson et al. Drug Intell Clin Pharm 1987; 21: 346-351. Evaluation of Metronidazole Gel in Acne Rosacea

Design and enrollment of these two published studies (Nielsen's and Aronson's) have been given above (see Section 7). Both articles were presented as single paragraphs in the Clinical Data Section (Item 8) of this NDA. They were presented in detail in Item 6 of the NDA and reviewed by Biopharm. The following was described in Item 8:

1. In the Nielsen study, after 1 month of daily treatment with metronidazole 1% cream in rosacea patients, traces of metronidazole (<20 ng/ml to 45 ng/ml) were detected in the plasma in 10/40 subjects. No adverse events were reported, but the investigators stated that the cream and its vehicle both had a drying effect on the skin.

2. In the Aronson study, plasma metronidazole levels up to 24 hr after application of 1 Gm metronidazole 0.75% gel on the face in rosacea patients were mostly negative (<25 ng/ml), with C_{max} of 40.6 ng/ml (about 20% of the C_{max} after receiving oral metronidazole solution and correction for difference in dose).

Comment These two studies suggest that percutaneous absorption of topical metronidazole after application to facial skin of rosacea patients (single dose or up to one month treatment) is very low.

10.1.9.2 Dermal Safety Studies

10.1.9.2.1 Study ICP#63/0001 A Forty-four Day Cumulative Irritancy Evaluation of Three Topical Metronidazole Formulations

Details on this study including design, enrollment, PK data and adverse events have been given above (see 10.1.9.1.3). Most of the test sites in the 24 subjects gave negative reactions at all times over the 44 day study period. Equivocal or positive results of irritancy evaluation are as follows:

<u>Formulation</u>	<u>Skin Condition</u>	<u>Number with Score* of</u>	
		<u>(+)</u>	<u>(1)</u>
Metronidazole 0.5% cream	Intact	1	4
Metronidazole 1% cream	Intact	5	4
Metronidazole 2% cream	Intact	4	2
Placebo cream	Intact	4	2
Metronidazole 2% cream	Stripped	6	8
Placebo cream	Stripped	7	2

*Scoring system: 0=negative, +=equivocal, 1=erythema, 2=erythema & induration, 3=erythema, induration and vesicles, 4=erythema, induration and bullae. No reaction had score above 1.

The test sites were irradiated (350-375 nm) for phototoxicity after removal of the last patches on day-44. The test sites were examined one day later (except for subject who was seen 2 days later). One out of the 24 subjects showed slight erythema at both stripped sites (metronidazole 2% and vehicle) which resolved within one day.

Comment

1. Except for metronidazole 2% cream on stripped skin, irritation appears to have been minimal and lacking in a clear-cut dose-response relationship.
2. The phototoxicity study was done using UVA. The absorption spectrum for metronidazole showed primarily absorption in UVC with extension into UVB.
3. The test sites should also have been evaluated 20 to 60 minutes after irradiation for more immediate reactions.

10.1.9.2.2 Study DL-6027-9611 Repeated Insult Patch Test (Jordan-King Modification of the Draize Procedure) for Contact Sensitization Potential of Metronidazole cream 1%

This study was performed under

in 1996 using the current formulation (NORITATE® cream).

Metronidazole 1% cream (0.2 ml each) was applied under occlusion using a non-woven cotton pad (Webril®) to the lower back for 48 hrs (72 hrs for weekends). Three applications were made per week for 3 weeks for induction. After induction phase, there was a rest phase for 2 weeks. Subjects were then challenged with metronidazole 1% and vehicle creams at naive sites on upper back for 48 hours. An optional rechallenge with sample or sample components might be made to a naive site to confirm reactions indicative of sensitization. Examination of induction or challenge patch site(s) were made 48 or 72 hours after application.

Two hundred and fifty-eight healthy subjects enrolled and 240 completed the study. Nine did not return during induction and 7 during challenge phase. Two were terminated for protocol violation (missing two visits). There were 68 males and 190 females; 237 whites, 9 Asians, 6 Hispanics and 5 blacks (one with race n/a) and the age range was 20-81. The following Table summarizes the scoring in the subjects:

Scores	Application Number at Induction Phase									Challenge		
	1	2	3	4	5	6	7	8	9	mu*	A*	A**
Metronidazole 1% cream												
0	247	221	216	196	210	221	211	217	216	34	229	219
1	5	28	34	46	29	24	33	24	23	8	13	16
2	0	0	0	0	0	1	0	1	0	0	1	0
3	0	0	0	0	0	0	0	0	0	0	0	1
P	0	1	2	12	12	12	16	8	17	4	0	11
Vehicle cream												
0	**	-	-	-	-	-	-	-	-	-	223	215
1	-	-	-	-	-	-	-	-	-	-	19	21
2	-	-	-	-	-	-	-	-	-	-	1	1
3	-	-	-	-	-	-	-	-	-	-	0	1
P	-	-	-	-	-	-	-	-	-	-	0	16

*mu=make up session, A=first scoring of challenge site (48 hr) and A'=second scoring of challenge site (72 hr). Scoring system: 0=no reaction seen, 1=mild=faint macular erythema, 2=moderate=definite macular erythema and 3=strong to severe=intense macular erythema; P=papules.

**Vehicle cream not used in induction phase.

There were no serious or unusual drug-related adverse events. Unrelated adverse

events included: herniated disk and ear infection in one subject and sinus infection in another. There were no Clinical Laboratory tests in this study.

Comments

1. It is difficult to interpret the mild erythema and presence of papules in some subjects during the induction phase in the absence of a vehicle control. However, in the majority of instances, no irritation reaction was elicited.
2. The challenge reactions of metronidazole 1% cream appear to be similar to those with vehicle cream. These consisted primarily of mild erythema, with papules (metronidazole 11, vehicle 16) and edema (metronidazole 1, vehicle 1) in some subjects occurring at 72 hr but not at 48 hr. However, none showed vesicles, bullae or induration. This study has not demonstrated that metronidazole 1% cream is a sensitizer.

10.1.9.2.3 Study DL-6029-9617 Phototoxicity Bioassay for Metronidazole 1% Cream

This study was done at

in 1996. The lower or mid-back was tested with 80 mg of metronidazole 1% or vehicle cream per site (2x2 cm), each for two sites. After the test material dried, the sites were covered with equal squares of non-woven cotton cloth for 24 hr. One set of patches was then removed and the sites exposed immediately to 20 J/cm² of UVA (320-400 nm) and visible light while the other set served as control. The reactions were scored at 0, 24 and 48 hrs after irradiation.

Twenty-one healthy Caucasian subjects enrolled: males 11 and females 10, with age range of 18-29. One male aged 20 dropped from study for personal reasons. There were no adverse events or unanticipated adverse reactions reported. Under the conditions of testing, phototoxic potential of metronidazole 1% cream was not detected.

Comment The phototoxicity study was done using UVA. The absorption spectrum for metronidazole showed primarily absorption in UVC with extension into UVB.

10.1.9.2.4 Study DL-6029-9618 Photocontact Allergenicity Assay for Metronidazole 1% Cream

This study was also done at

in 1996. During induction phase, 80 mg of test material was applied to 2x2 cm² sites over the lower back (20 mg/cm²) and left occluded for 24 hrs. The sites were then exposed to 3 MED (minimal erythema doses) from a xenon arc solar simulator. The MED was to be predetermined by exposure to a series of 25% incremental doses and reading 24 hr later. The sequence of test application and 3MED exposure 24 hr later was repeated at the same site for a total of 6 exposures (2 exposures/wk for 3 wks). After an 11-day rest, challenge was done at a naive site on the opposite side of the back. About 80 mg of test material was applied over a 2x2 cm² area for 24 hr under occlusion. The site was then exposed to 0.5 MED of solar-simulated radiation (SSR) plus 4 Joules/cm² of UVA obtained from the filtered xenon arc solar simulator with filter to eliminate UVB. An unirradiated site treated with the test product served as control. The sites were examined 48 and 72 hr after irradiation.

Twenty-nine healthy Caucasian subjects enrolled: males 14 and females 15, with age range of 18-23. There were no adverse events or unanticipated adverse reactions reported. Under the conditions of testing, photocontact sensitization potential of metronidazole 1% cream was not detected.

Comment The challenge was done using UVA. The absorption spectrum for metronidazole showed primarily absorption in UVC with extension into UVB.

10.1.10 Withdrawal Phenomena/Abuse Potential Not known.

10.1.11 Human Reproduction Data

Saihan and Burton noted that systemic metronidazole was used for trichomoniasis in pregnant women for 20 years and had not been associated with an increase in stillbirths or malformations, even when given in the first trimester (*Br J Dermatol* 102:443, 1980). In addition, Roe reported analyzing a follow up study at Hammersmith Hospital in London between 1971 and 1976 and noted no increased risk of birth defects in 597 pregnant women treated for trichomonas infections, vs 283 untreated women and 9000 uninfected control women (*Surgery* 93: 158, 1983). One study, the Collaborative Perinatal Project, found a suggestion of increased risk based on 4 birth defects instead of 2 expected among 31 pregnancies exposed in the first trimester (relative risk=2) (in *Birth Defects and Drugs in Pregnancy*. Littleton, MA. Publishing Sciences Group pp. 298-302, 1977). The current status is that although there is no clear evidence that metronidazole is a teratogen, systemic use is advised against in the first trimester. However, since untreated trichomoniasis may carry a risk of preterm delivery, use in second and third trimesters may be acceptable if other therapies have failed.

The U.S. development program for NORITATE® cream excluded females of childbearing potential unless they used adequate birth control. The Canadian studies for metronidazole 1% cream excluded patients in pregnancy or lactation. Thus, there are no human reproduction data for metronidazole 1% cream formulation from the submitted clinical trials. As systemic exposure to metronidazole is minimal with use of NORITATE® cream, it is not expected to carry a significant risk to the fetus.

10.1.12 Overdose Experience

No experience with NORITATE® overdose is known. As one tube of this drug product will contain 300 mg metronidazole, which is one order of magnitude less than the highest recommended daily dose for the oral dosage form (2.25 Gm/d), any toxicity resulting from acute exposure to metronidazole by ingestion of the content of a tube is unlikely, although toxicity due to the excipients may need to be considered.

10.2 Review of Systems

Systemic administration of metronidazole may be associated with symptoms of gastrointestinal upset and neurologic disorders including seizures and peripheral

neuropathy, which has been characterized by numbness or paresthesia of an extremity. Rodent studies have revealed evidence of carcinogenic activity, including the possible promotion of lung, liver, lymphoid and mammary tumors. A mild leukopenia has been observed during metronidazole administration; however, no persistent hematologic abnormalities attributable to metronidazole have been observed.

In the clinical studies on NORITATE® topical cream 1% in the treatment of rosacea, possibly treatment-related adverse events were primarily local, including (1) "application site reaction", (2) symptoms of skin and appendages, (3) symptoms of the eyes and (4) paresthesia. However, some events were not necessarily considered by the Investigator as being treatment-related and the description in the data listing or CRF might be inadequate. They are therefore considered as possibly related in this review. The following review of systems is based on the U.S. and Canadian phase 3 clinical trials.

10.2.1 Dermatological

"Application Site Reaction" This term is vague and remains to be defined. One patient treated with metronidazole 1% cream qd and three with metronidazole 1% cream bid developed this reaction, giving an incidence of 0.5% and 1.5% respectively.

Adverse Events of Skin and Appendages Only one case of "comedonal acne flare" was listed as being related to metronidazole 1% cream qd treatment, whereas there were 14 related adverse events with the bid regimen (dermatitis 1, contact dermatitis 3, dry skin 1, photosensitivity reaction 1, pruritus 5, rash 1 and "skin disorder" 2). There were also one case of rash and 3 of "skin disorder" with the qd regimen but they were not considered by the Investigator as being related. No evidence of an allergic component has been presented for the contact dermatitis in the patients who used topical metronidazole.

Erythema Two patients who used metronidazole 1% cream bid developed erythema under "body as a whole". It is unclear as to the location and extent of the adverse event.

Condition (rosacea) aggravated One patient given metronidazole 1% cream had rosacea condition aggravated. Although this was not considered related to treatment, this possibility and the possibility of treatment failure both merit consideration.

10.2.2 Neuropsychiatric

One patient treated with metronidazole 1% cream bid developed psychosis. No details on concomitant alcohol intake has been given. It is difficult to evaluate the relationship of this event with treatment.

Paresthesia occurred in one patient treated with qd regimen and 4 with bid regimen of metronidazole 1% cream. These cases did not result in discontinuation and no detailed description for the location or nature of the paresthesia is available.

10.2.3 Special Senses

Conjunctivitis associated with rosacea was one of the exclusion criteria for the clinical studies. Two patients given metronidazole 1% cream qd and one given the cream bid developed conjunctivitis. Although the conjunctivitis in the patients given metronidazole 1% cream qd were not considered related to treatment, these three cases must be considered "possibly" related until details prove otherwise.

10.2.4 Others

There is no evidence of leukocyte disorder or tumor development in association with metronidazole use in the phase 3 U.S. and Canadian trials.

10.3 Summary of Key Adverse Findings

The pertinent adverse events associated with use of topical metronidazole cream have been primarily local with symptoms at the application site (face) and possibly development of irritant contact dermatitis.

11 Labeling Review

4 Pages (54-57)

Deleted

12 Conclusions

This application is subjected to benefit-risk analysis with the following conclusions:

1. NORITATE® cream (metronidazole 1% cream) qd is effective in the treatment of rosacea (a) with reduction of erythema, papule and total lesion counts and (b) as evaluated by physician's global.
2. Metronidazole 1% cream qd is well tolerated by patients with rosacea and has low percutaneous absorption such that systemic exposure is minimal.
3. The qd and bid regimens do not differ significantly in efficacy but the qd regimen is associated with a slightly lower incidence of both total and treatment-related adverse events.
4. As the qd regimen would provide a lower dose than currently approved dosing for topical metronidazole (bid dosing for metronidazole 0.75% cream or gel), it is anticipated that the proposed qd regimen for NORITATE® cream may yield a greater benefit risk ratio than other marketed topical metronidazole products in the treatment of rosacea.

13 Recommendations

13.1 Approval, Approvable, Non-Approval

This application is approvable but the Applicant needs to address the label and the deficiency list (see 13.4).

13.2 Phase 4 Studies

No phase 4 studies are recommended.

13.3 Labeling

It is recommended that the Applicant modify the label as recommended in Section 11 of this review.

13.4 Other

1. The type of sunscreen used in U.S. pivotal trials and a listing of patients who used sunscreen should be provided.
2. An adequate accounting of the noncompliant patients in U.S. pivotal studies and details of their concomitant use of antibiotics would be required for exclusion in analysis.
3. As the qd and bid regimens of NORITATE® have not shown significant differences in efficacy, and the bid regimen did not demonstrate superiority over placebo in DL6027-9510, an analysis between the metronidazole qd and placebo bid arms would be needed.

A-S. Ko 6-13-97 H. S. Ko. revised 7-7-97

Hon-Sum Ko, M.D.

cc: NDA 20-743
HFD-540
HFD-340
HFD-540/CSO/Cintron
HFD-540/CHEM/Higgins
HFD-540/PHARM/Alam
HFD-520/BIOPHARM/Kumi
HFD-715/BIOMETRICS/Farr
HFD-540/MO/Ko

CT 6/24/97

As above with changes
in 7/7/97 revision.

FW 7/8/97